Clinical experience of dispensary observation for ten thousand patients with Hashimoto's autoimmune thyroiditis: Some features of aetiology, manifestations, treatment and comorbidity*

Yu. I. Stroev

St. Petersburg State University,
7–9, Universitetskaya nab., St. Petersburg, 199034, Russian Federation

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Chronic autoimmune thyroiditis is the most common autoimmune disease and the main cause of hypothyroidism in the world. From March 14, 2011 to present we have systematically monitored in our outpatient dispensary center over 10,000 persons aged 1 year to 87 years with a newly diagnosed autoimmune thyroiditis (having totally ≈19,500 of their dynamic observations). In this article we address some features of autoimmune thyroiditis, namely aetiology (possible genetic predisposition and the role of some triggers, including excessive iodine intake), early manifestations of hypothyroidism, comorbidity (such as stigmata of non-syndromal marfanoid phenotype, metabolic syndrome, pituitary prolactinomas, lymphomas and some other malignancies) and treatment strategy (the proper time to start therapy, adjustment of the doses of Levothyroxine, monitoring follow-up dinamics of the disease and possible complications of the therapy). Hashimoto's thyroiditis in our experience looks like important cause of hyperprolactinemia and female/male infertility and essential prerequisite of early adolescent metabolic syndrome, causing precaucious metabolic senescence in subsequent life.

Keywords: Hashimoto's autoimmune thyroiditis, iodine, hyperprolactinemia, hypothyroidism, obesity with rose strias, marfanoid phenotype, metabolic syndrome, infertility, levothyroxine.

Chronic autoimmune thyroiditis (AIT) is the most common autoimmune disease and the main cause of hypothyroidism in the world. Discovered by Hakaru Hashimoto 107 years ago in most seafood-consuming area of Japan, it turned out to be not an endemic or exotic, but a global medical and social problem for all ages and health care sectors — from Paediatrics to Geriatrics. Its frequency in the Russia was estimated up to 45 cases per 1000 people. After the Chernobyl accident, the incidence of AIT among persons subjected to uncontrolled iodine prophylaxis increased by hundreds of times.

From March 14, 2011 to present we systematically monitored in our outpatient dispensary center over 10,000 persons aged 1 year to 87 years with a newly diagnosed AIT

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(having totally ≈19,500 of their dynamic observations). The AIT is a multifactorial disease. Patients often have close relatives with the autoimmune disorders of the thyroid gland and other organs. AIT usually does not develop without the influence of provoking factors (infections, adjuvant-like stimulators of immune system, estrogen abuse, trauma or even rough palpation of the thyroid, unjustified thyroid biopsy, etc.) [1]. Uric acid also can act as an adjuvant. Our findings suggest a two-way relationship between AIT and hyperuricemia [2]. A pivotal aetiological factor of AIT is the excessive iodine intake with food, dietary supplements and medicines for obvious adjuvant action of this trace element. For example, one amiodarone tablet contains a person's annual allowance for iodine, and therefore this anti-arrhythmic medicine often provokes AIT. An excess of iodine is especially harmful for thyroid gland which is already unhealthy. According our data, it may suppress physiological compensatory response of pituitary for emerging hypothyroidism [1]. For the AIT diagnosis, a clinical criterion (diffuse enlargement of the thyroid gland for no other reason) is used in combination with any of the three laboratory criteria (presence of elevated level of antithyroid autoantibodies, cytologically verified mononuclear infiltration of the thyroid gland, as well as typical ultrasonographic or thermographic thyroid image with heterogeneous structure and small nodes). The hypothyroidism develops in AIT without bright symptoms and often is missed by diagnosticians. The complaints arise when AIT has been already progressed, hence it is often suspected after occasional thyroid ultrasonography.

According our experience, an early sensitive sign of hypothyroidism is regular bites of cheek and tongue (*morsicatio buccarum et linguae*) and teeth impacts on tongue appeared without any stomatological reasons [3]. Unlike many other autoimmunopathies, AIT is characterized by the paradoxical nature of autoimmune processes: Hypothyroidism can transform in its course into episodes of hyperthyroidism (hashitoxicosis) and vice versa. The manifestations are determined by prevail of effects of different co-existing autoantibodies, both thyro-stimulating and thyro-blocking. That's why dynamics of endocrine disorder commonly do not correspond to their titers [1]. For example, in the first visit 3.5 % of our patients with a clinic of overt AIT and slight hypothyroidism, did not display diagnostic titers of anti-thyroid antibodies, which appeared just later. The vast majority of patients with AIT (up to 80 % among our cohort) have stigmata of non-syndromal marfanoid phenotype; even classic proven Marfan syndrome was registered among them 70 times more frequently than in local population. We have determined in AIT elevated levels of TGFβ1–2 and leptin, like in full Marfan syndrome. Both cytokines may facilitate development of AIT [1; 4]. Gradually progressing untreated AIT produces overt hypothyroidism, which is literally "written" on the faces of advanced patients. Unfortunately, many practitioners prefer to diagnose AIT only by blood tests, and just do not pay attention to the classic symptoms of hypothyroidism (drowsiness, dry skin, hyperkeratosis of the elbows, knees and soles, pastiness of the face and limbs, teeth imprints on the tongue, persistent bites of the swollen cheeks, constipation, and hair loss). If something of that is noticed, it is interpreted as a sign of other diseases [3]. Persons with hypothyroidism constantly complain of chilliness and, as a rule, during cool season go to bed in their socks, which can be an early symptom of thyroid insufficiency. Even infectious diseases in them proceed with low-normal body temperature. Because of thyroid influence on expression of many genes and due to extrathyroid targets of its autoimmunity, AIT is very often combined with other autoimmune diseases (Schmidt syndrome, pernicious ane-

mia with atrophic gastritis, immune thrombocytopenic purpura, hypoparathyroidism, Sjogren's syndrome etc.). Half of patients suffering from AIT are risky for the development of metabolic syndrome, which is manifested by the formation of obesity, dyslipidemia, insulin resistance, arterial hypertension, palmar sclerosis and other components. Early complicated metabolic syndrome is very typical for people who displayed in childhood and youth AIT comorbid with Simpson–Page syndrome (obesity with rose striae). We observed clinically or anamnestically this syndrome presenting in 24 % of our AIT cohort, although its prevalence in local population is only 1.5 % [4].

Both hypothyroidism and certain autoantibodies may affect mental health in AIT (from phobias to "hypothyroid madness"). Up to 3 % of all "mental" patients have unrecognized hypothyroidism, some of those with psychotic symptoms may have in fact autoimmune encephalitides [5]. The metabolism of vitamin D3 is impaired in AIT, which is accompanied by tendency to hypocalcaemia and implicated for such frequent symptoms as seizures, hair loss and onychodystrophy [1; 3]. Because of prolactoliberin action of thyroliberin, hypothyroidism in AIT is always accompanied by hyperprolactinemia, even in children and adolescents, forming crucial vicious circle in AIT pathogenesis, because prolactin in turn stimulates autoimmunity [3; 6].

Hyperprolactinemias either caused by prolactinomas or by anti-psychotics — are associated with increased incidence of AIT [7]. AIT in our practice is often combined with pituitary prolactinomas or non-homogenous MRI image of pituitary, suspicious for hypophysitis (in 40 % of cases). Supposedly, AIT-caused chronic hyperprolactinemia may be the risk factor both for prolactinoma and autoimmune hypophysitis. The AIT is a benign disease, but patients are at an increased risk of lymphomas and some other malignancies. Up to 5 % of our AIT cohort developed lymphocytic leukemia, B-cell lymphomas or thyroid papillary cancer. Treatment of AIT is to continue lifelong. Thyroid hormones provide not only replacing, but also immunomodulating effect, because they suppress hyperprolactinemia and facilitate the apoptosis of lymphocytes, thus having (without general immunosuppression) noticeable therapeutic effect on anti-thyroid and another, concomitant autoimmune disorders (e.g. immune thrombocytopenic purpura and psoriasis) [8]. It is advisable to start treatment not waiting for so-called "diagnostic titers" of autoantibodies, because thyroid damage is established mostly not *via* antibodies, but by cell-mediated autoimmunity. Moreover, increase in autoantibody titers may be very transient. The doses are selected individually, under the control of TSH and thyroid hormones with follow-up of clinical dynamics. We have been observing a woman with AIT, in whom the optimal dose of Levothyroxine was selected as large as 800 mcg per day for many years. In case of cardiac arrhythmias or sleeplessness, we recommend splitting daily dose of Levothyroxine and taking it twice in halves [9]. While treating AIT with hypothyroidism, the optimal TSH range to achieve is 0.5–1.5 μU/ml, typical for most of healthy people. Abuse of iodides may reduce TSH level, not corresponding to the status of thyroid function. Therefore, we always recommend to AIT patients abstain from iodide-containing drugs, supplements and food and combine TSH and thyroid hormone monitoring. If an inexplicable decrease in the blood level of TSH is detected in the absence of hyperthyroid symptoms, the "iodine history" of a case should be clarified; also such patient has to be checked for TSH receptor autoantibodies [3; 8]. In hyperprolactinemia, an MRI study of the pituitary gland with contrast is recommended. In such cases, along with Levothyroxine, dopamine agonists will be needed. Hyperprolactinemia is an important cause of reproductive failure,

sexual orientation disorders. It may cause in AIT female and male infertility. Early diagnosis and appropriate treatment of AIT is a way to keep and restore patient's reproductive potential [6].

References

1. Stroev Yu. I., Churilov L. P., Serdyuk I. Yu., Mudzhikova O. M. Autoimmune Thyroiditis: A New Comorbidity of the Most Prevalent Endocrine Disease, Its Prevention and Prediction. In: Poletaev A. B. (ed.), *Physiologic Autoimmunity and Preventive Medicine*, Bentham Science Publishers, Oak Park a.e. 2013, pp. 208–233.
2. Goncharova E. S., Pestun E. M., Poyarkova A. I., Stroev Yu. I., Churilov L. P. Uric acid, gout and autoimmune thyroiditis: From E. S. London — till nowadays. *Clin. Pathophysiol*., 2018, vol. 24, no. 4, pp. 56–67. (In Russian)
3. Stroev Yu. I., Churilov L. P. Hashimoto's autoimmune thyroiditis, its consequences and comorbidity. In: Shoenfeld Y., Meroni P. L., Churilov L. P. (Eds). *Guide in Autoimmune Diseases for General Medical Practice,* St. Petersburg, Medkniga-ELBI Publishers, 2017, pp. 298–325. (In Russian)
4. Churilov L. P., Stroev Yu. I., Serdyuk I. Yu., Kaminova-Mudzhikova O. M., Belyaeva I. V., Gvozdetsky A. N., Nitsa N. A., Mikhailova L. R. Autoimmune thyroiditis: Centennial jubilee of a social disease and its comorbidity. *Pathophysiology*, 2013, vol. 21, pp. 135–145.
5. Churilov L. P., Sobolevskaia P. A., Stroev Yu. I. Thyroid Gland and Brain: Enigma of Hashimoto's encephalopathy. *Best Pract. & Res. Clin. Endocrinol. & Metab.,* 2019, vol. 33, no. 6, 101364. https://doi.org/10.1016/j.beem.2019.101364.
6. Churilov L., Stroev Yu., Ali N., Kaledina E., Utekhin V., Donchenko E. Hyperprolactinemia in pathogenesis of autoimmune infertility. Abstract Auto1-0527*). 11th International Congress on Autoimmunity*, 14-16 May 2018. Lisbon.
7. Poyraz B. C., Aksoy C., Balcıoğlu I. Increased incidence of autoimmune thyroiditis in patients with antipsychotic-induced hyperprolactinemia. *Europ. Neuropsychopharmacol.,* 2008, vol. 18, no. 9, pp. 667–672.
8. Stroev Yu. I., Churilov L. P. Autoimmunity thyroid function and aging: New aspect of understanding. *Jap. J. Pathophysiol*., 2008, vol. 17, no. 2, p. 35.
9. Stroev Yu. I., Churilov L. P., Sadov S. A., Zhao Wenlong. Thyroid diseases in senior citizens of St. Petersburg. *Wiener klinische Wochenschrift,* 2009, vol. 121, no., pp. 71–72.

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Author's information:

Yuri I. Stroev — MD, PhD, Associate Professor; svetlanastroeva@mail.ru